UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/544,910	04/07/2000	Yadong Huang	06510/121US1	2429

24353 7590 01/02/2008

BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
01/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/544,910	HUANG ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-8 and 11-35* is/are pending in the application.

4a) Of the above claim(s) *12-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 5, 2007 has been entered.

Status of Claims

Currently, claims 1, 4-8, and 11-35 are pending. Claims 12-35 have previously been withdrawn as being drawn to non-elected inventions. Accordingly, claims 1, 4-8, and 11 are currently under examination on the merits.

Response to Arguments

Applicant's arguments filed on December 5, 2007 have been fully considered but they are not persuasive. See below for reasons.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-8, and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following are the assessment of each factor listed above.

(A) The breadth of the claims

The claims are drawn to *in vivo* antisense-mediated gene therapeutic methods for reducing the plasma level of VLDL in a host by at least two folds or treating hyperlipidemia in a

host, wherein the methods comprise administering an effective amount of an antisense nucleic acid that reduces the expression of apoE3.

(B) The nature of the invention

The nature of the instantly claimed invention is regarded as "systemic gene therapy" in the art.

(C) The state of the prior art

The earliest date sought in the instant application is April 12, 1999. There was no prior art teaching that demonstrated that making a therapeutic antisense compound and administering it to a subject systemically for a therapeutic outcome is considered routine. In fact, a post-filing review article by Ponder (*Trends in Cardiovascular Medicine,* August 1999, 9:158-162) explicitly teaches, "Successful long-lived systemic gene therapy has three requirements: efficient gene transfer, appropriate expression, and long-term survival of transduced cells." See page 158. The article further teaches that hepatocytes are an obvious target for systemic gene therapy because they have direct contact with the blood and that no therapeutically effective delivery mechanism has been reported as of August, 1999. Further, as previously pointed out in the Office action dated December 8, 2006, the difficulty and complications arising from antisense-mediated gene therapeutics were fully and widely recognized across the antisense industry, which consequently resulted in decreased interest in pursuing antisense compounds as therapeutic agents. See page 5 of the Office action and the cited article by Scherer et al. (*Nature Biotechnology,* 2003, 21:1457-1465, citation of record).

Applicant continues to make mere allegations that the state of the art of making and using antisense nucleic acids was well-developed, and in so doing, provides a number of references that are not directly related to the instantly claimed target gene or the methods. In other words, applicant has failed to show factual, scientific evidence as to how or why the state of the prior art in relation to the claimed methods was well-developed.

(D) The level of one of ordinary skill

Consistent with the state of the prior art in the instantly claimed gene therapeutic methods, the level of one of ordinary skill in the art at the time the invention was made was considerably low. Applicant argues that a relevant ordinarily skilled artisan is "required to keep abreast of the latest technology through continuing education and reading scientific journal articles" and therefore, "the skill level of those designing and using antisense nucleic acids assays was high as of the April 12, 1999 priority date." It appears that applicant refers to a different invention because the instantly claimed invention is not directed to a method of designing and using antisense nucleic acids assays. Again, as set forth in factors (A) and (B) above, the instantly claimed invention is purely therapeutic with specifically recited limitation of "reducing the plasma level of VLDL in a host by at least two folds" and "treating a host suffering from a disease condition". Further, as stated above in factor (C), there was no prior art teaching that pertains to the claimed methods, which would have provided sufficient guidance to one of ordinary skill in the art as to how to make the claimed antisense nucleic acid that functions as claimed in the instant case and how to use it to achieve the claimed therapeutic effects.

(E) The level of predictability in the art

The unpredictable pharmacokinetics of nucleic acid drugs in a living organism, including the claimed antisense nucleic acid, was well known in the art at the time the invention was made. Applicant argues that since Mercola et al. teach that "oligodeoxynucleotide experiments which yield promising results in tissue culture can be generalized to the *in vivo* setting by development of clones of cells bearing plasmid-derived antisense RNA against the same target", the claimed invention is fully enabled. This argument appears puzzling since the instant specification provides no working example comprising antisense oligonucleotides in tissue culture, and therefore, there is no data to draw a generalized *in vivo* therapeutic outcome regarding the claimed antisense nucleic acid.

(F) The amount of direction provided by the inventor

With regard to the claimed antisense-mediated gene therapeutic methods of treating hyperlipidemia, the inventors of the instant application did not provide any substantive, objective, scientific, and clinical guidance necessary to achieve the claimed therapeutic effects (i.e., reducing the plasma level of VLDL by at least two folds, treating hyperlipidemia).

Again, the inventors did not even provide sufficient guidance as to which antisense nucleic acid has the greatest potential to reduce the plasma level of VLDL in a host by at least two folds, let alone showing the appropriate, optimal design of the claimed antisense nucleic acid, which will result in at least two-fold reduction in the plasma VLDL expression level in a living organism. That is, the teachings disclosed in the specification are entirely prophetic and generic.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004): "Nascent technology, however, must be enabled with a specific and useful teaching. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." See also MPEP §2164.03. (emphasis added)

Applicant contends that the instant application provides data showing that overexpression of apoE causes hypertriglyceridemia by stimulating VLDL production. From this statement, applicant deduces that "reducing the plasma level of active apoE ***will*** also reduce the plasma level of VLDL." First, contrary to applicant's contention, the instant specification does not provide date showing the causal relationship between apoE and hyperlipidemia/VLDL production. The specification show "correlative relationship" between apoE and hyperlipidemia/VLDL production. "Correlation" is not same as "cause-and-effect". Further, even

if there was a causal relationship as applicant alleges, the specification does not provide any data showing that an antisense nucleic acid targeted to apoE3 indeed reduces the plasma level of VLDL by at least two folds in a host and treats hyperlipidemia.

(G) The existence of working examples

As repeatedly pointed out in prior Office actions, the instant specification is completely devoid of working examples commensurate in scope with the claimed invention.

Applicant argues, "Compliance with the enablement requirement under 35 U.S.C. §112, first paragraph, does not require or mandate that a specific example be disclosed." Contrary to applicant's argument, lack of a working example is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. Again, the antisense-mediated systemic gene therapy was and still is an unpredictable art and was an underdeveloped art at the time of the invention. See factor (C) above. In the instant case, there is not even a single *in vitro* working example, let alone an *in vivo* example comprising an antisense nucleic acid. Further, no specific antisense nucleic acid claimed in the instant case was actually made and tested in the instant specification. As such, there is no scientific ground based on which one of ordinary skill in the art would be able to extrapolate a reasonable conclusion about the claimed *in vivo* therapeutic methods with the requisite therapeutic effects.

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure

Again, not even a single species of antisense nucleic acid that indeed reduces plasma level of VLDL in a host by at least two folds. Even more, not even a single species of antisense nucleic acid that reduces apoE3, which might harbor the potential to be used in the claimed methods, is described in the specification. Applicant argues, "one of skill in the art would be able to perform the experiments as a matter of routine to determine the active nucleic acids", and therefore, the amount of experimentation required to make and use an antisense nucleic acid that reduces expression of apoE would not be undue. This argument is irrelevant and out of scope in the instant case. As discussed at length above, the claimed methods comprise the step of administering an antisense nucleic acid to a host, which should necessarily reduce plasma level of VLDL by at least two folds and treat hyperlipidemia, as claimed in the instant case. The individual assessment of the factors (A)-(G) and the combined view of the totality of the factors suggest that one of ordinary skill in the art would not have been able to practice the entire scope of the claimed invention without undue experimentation at the time of the invention.

Determination of Enablement Based on Evidence as a Whole

To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. As discussed above, applicant has failed to establish factual evidence that supports applicant's mere allegation that the claimed invention in its entirety was fully enabled at the time of the invention.

See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991), in which it was clearly presented that a rejection under 35 U.S.C. 112, first paragraph for lack of enablement

was appropriate, given the relatively incomplete understanding in the biotechnological field involved, and the lack of a reasonable correlation between the narrow disclosure in the specification and the broad scope of protection sought in the claims.

In view of the totality of the factors listed above and the reasons stated above, the claims are rejected as failing to comply with the enablement requirement as set forth in the first paragraph, 35 U.S.C. 112.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner
Art Unit 1635